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ECBC-TR-1473

SCALED-UP SYNTHESIS: SALTS OF CARFENTANIL AND REMIFENTANIL

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July 2017

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PREFACE

The work described in this report was started in June 2015 and completed in July 2016.

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SCALED-UP SYNTHESIS: SALTS OF CARFENTANIL AND REMIFENTANIL

1. INTRODUCTION

4-Anilidopiperidines are potent synthetic opioids that are employed as analgesics worldwide.¹ Janssen, Van Daele, Niemegeers, Janssens, and their coworkers have produced many potent and clinically useful compounds.^{2–5} A potent, short-acting analog was later developed by Feldman et al.⁶ Some of these analgesics have been prescribed as potent sedatives for large animals (carfentanil) and humans (remifentanil).

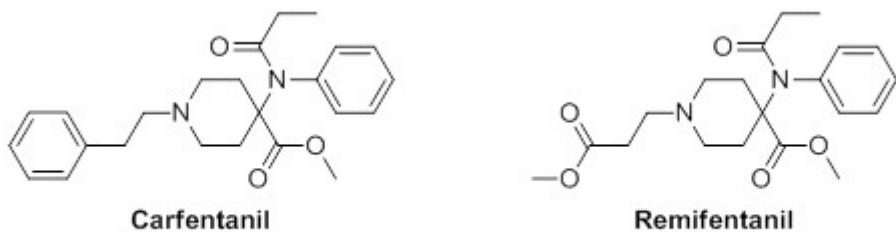


Figure 1. Structures of carfentanil and remifentanil.

A few of the pharmaceutically relevant salts of these compounds are carfentanil oxalate, carfentanil citrate, remifentanil oxalate, and remifentanil hydrochloride. The work presented demonstrates the multigram syntheses of these four salts.

2. CHEMISTRY

The syntheses of carfentanil and remifentanil are shown in Figure 2. The syntheses illustrated were derived from the literature cited previously. The syntheses began with commercially available 1-benzyl-4-piperidone. Imine formation was followed by hydrocyanation across the carbon–nitrogen double bond to produce compound 1. Amide bond formation through the action of propionyl chloride generated compound 2. Crude compound 2 was treated with methanolic hydrogen chloride to transform the nitrile into a methyl ester. Purification was affected by the precipitation of oxalate salt 3. No flash chromatography was performed over these three chemical transformations. Transfer hydrogenation, which employed ammonium formate as the hydrogen source, was applied to compound 3 and produced free amine 4. After the basic workup, the amine 3 was alkylated with phenylethyl chloride to provide the free base carfentanil. A Michael Addition, which employed methyl acrylate, was performed on the same free amine 4 to provide remifentanil. Individually, treating these two opioids with the appropriate acid produced carfentanil oxalate, carfentanil citrate, remifentanil oxalate, and remifentanil hydrochloride.

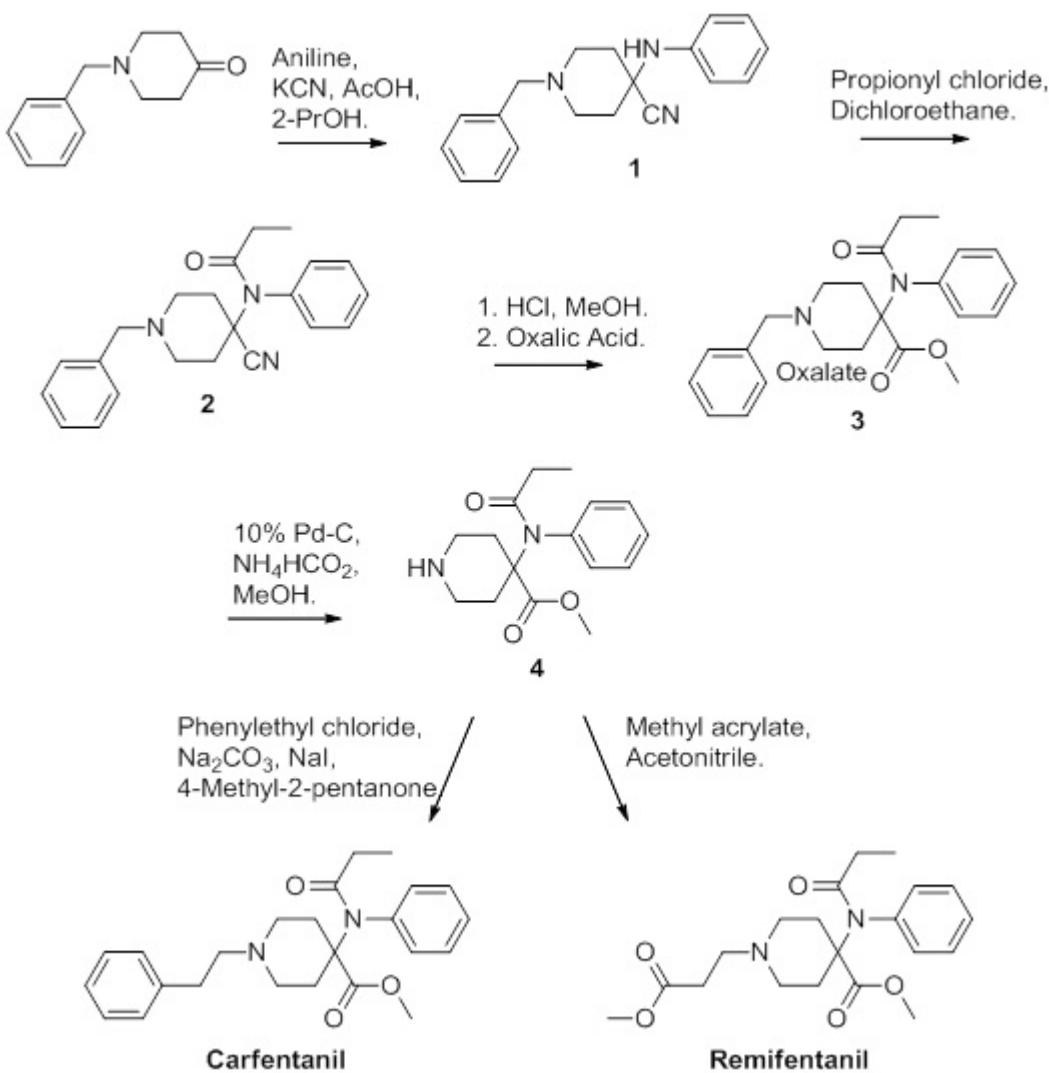


Figure 2. Synthesis of carfentanil and remifentanil.

3. EXPERIMENTAL PROCEDURE

Starting materials were purchased from Aldrich Chemical Company (Milwaukee, WI). Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL 400 MHz spectrometer (JEOL USA, Inc.; Peabody, MA), and chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane.

3.1 Compound 1

1-Benzyl-4-piperidone (25.00 g, 0.132 mol); oven-dried, powdered potassium cyanide (11.70 g, 0.180 mol); and distilled aniline (17.00 g, 0.180 mol) in 180 mL of isopropanol were cooled in an ice bath. Acetic acid (25 mL) was added dropwise to the mixture, and the addition funnel was rinsed with 20 mL of isopropanol. The solution was heated at reflux for 4 h.

The mixture was allowed to cool to room temperature and poured over an ice (120 g)/concentrated ammonium hydroxide (115 mL) mixture. The aqueous solution was extracted three times with chloroform. The organic layer was washed with brine. The organic solution was dried with magnesium sulfate and filtered, and the volatiles were subsequently evaporated. The residue was recrystallized from isopropanol to provide 33.04 g of compound 1 as a pale yellow solid in an 86% yield. Compound 1: mp 145–147 °C; ¹H NMR (CDCl₃) δ 7.35–7.23 (m, 6H), 6.93–6.90 (m, 4H), 3.65, br s, 1H, 3.56 (br s, 2H), 2.81 (br d, 2H, *J* = 11.91 Hz), 2.46 (t, 2H, *J* = 10.30 Hz), 2.33 (d, 2H, *J* = 13.28 Hz), 1.93 (t, 2H, *J* = 10.30 Hz); ¹³C NMR (CDCl₃) δ 143.4, 138.1, 129.4, 129.1, 128.5, 127.4, 62.7, 53.2, 49.4, and 36.2.

3.2 Compound 3

Compound 1 (20.00 g, 68.64 mmol) was dissolved in 1,2 dichloroethane (260 mL) at room temperature under a nitrogen atmosphere. Propionyl chloride (31.80 g, 343.68 mmol) in 40 mL of 1,2 dichloroethane was added dropwise to the solution. The addition funnel was rinsed with 10 mL of 1,2 dichloroethane. The reaction mixture was heated at reflux for 20 h. The mixture was allowed to cool to room temperature, and volatiles were evaporated to provide a crude compound 2. The resulting solid was dissolved in 300 mL of 6.67 M methanolic hydrogen chloride. The solution was stirred at room temperature for 18 h. Water (320 mL) was added, and the solution was stirred at room temperature for 4 h. The methanol was evaporated, and the aqueous solution was basified to pH 7.5 with sodium carbonate. The aqueous mixture was extracted three times with chloroform. The organic layer was washed with brine. The organic solution was dried with magnesium sulfate and filtered, and the volatiles were subsequently evaporated to provide 32.90 g of a brown oil. The oil was taken up in 200 mL of hot isopropanol, and a solution of oxalic acid dihydrate (10.28 g, 80.00 mmol) in 200 mL of isopropanol was added. The mixture was cooled in the refrigerator, and the precipitate was then filtered. The solids were washed with cold isopropanol followed by diethyl ether. The solids were air-dried to give 27.60 g of compound 3 as a white powder in an 85% yield. Compound 3: mp 201–204 °C; ¹H NMR (CD₃OD) δ 7.48–7.42 (m, 6H), 7.32–7.30 (m, 4H), 4.23 (s, 2H), 3.78 (s, 3H), 2.43 (br d, 4H, *J* = 14.65 Hz), 1.96–1.87 (m, 6H), 0.90 (t, 3H, *J* = 7.33 Hz); ¹³C NMR (CD₃OD) δ 175.4, 172.6, 165.1, 138.2, 131.1, 130.1, 129.8, 128.9, 60.5, 59.9, 51.9, 48.9, 30.1, 28.5, and 8.1.

3.3 Carfentanil Oxalate

Compound 3 (10.00 g, 21.25 mmol) and ammonium formate (6.70 g, 106.24 mmol) were dissolved in 250 mL of methanol. The solution was sparged with nitrogen for 1 h. Palladium (10%) on carbon (2.00 g) was added to the solution, and the mixture was heated at reflux for 3 h. The mixture was allowed to come to room temperature and was stirred overnight. The mixture was filtered through celite, and the filtrate was concentrated. The residue was taken up in a chloroform and saturated sodium bicarbonate solution. The organic layer was separated, and the aqueous solution was washed two times with chloroform. The combined organic layers were washed with brine. The organic solution was dried with magnesium sulfate and filtered, and the volatiles were subsequently evaporated to provide 6.10 g of compound 4 as a brown oil. This crude material was used without further purification. Compound 4: ¹H NMR (CDCl₃) δ 7.39–7.34 (m, 3H), 7.28–7.25 (m, 2H), 3.75 (s, 3H), 2.95–2.89 (m, 2H), 2.79 (dt, 2H,

J = 12.82 and 3.89 Hz), 2.20 (br d, 2H, *J* = 12.36 Hz), 1.82 (q, 2H, *J* = 7.48 Hz), 1.71 (br s, 1H), 1.47–1.40 (m, 2H), 0.91 (t, 3H, *J* = 7.48 Hz); ¹³C NMR (CDCl₃) δ 174.2, 173.9, 139.4, 130.7, 129.4, 128.7, 63.2, 52.2, 43.0, 34.6, 29.1, and 9.2.

Compound 4 (6.00 g, 20.66 mmol), 2-phenylethyl chloride (3.80 g, 27.00 mmol), potassium carbonate (10.20 g, 73.80 mmol), and a catalytic amount of potassium iodide (0.60 g) were mixed with 300 mL of 4-methyl-2-pentanone and heated at reflux for 20 h. The mixture was allowed to cool to room temperature. The solids were filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in chloroform and 2 N aqueous sodium hydroxide. The organic layer was separated, and the aqueous solution was washed two times with chloroform. The combined organic layers were washed with brine. The organic solution was dried with magnesium sulfate and filtered, and the volatiles were subsequently evaporated to provide a brown oil. This material was chromatographed in two batches using a Grace Reveleris X2 flash chromatography system (Grace Discovery Sciences [part of W.R. Grace and Company], Deerfield, IL) with a gradient elution that had 0–3% of 95/5 methanol/ammonium hydroxide in dichloromethane to provide 6.50 g of carfentanil. Carfentanil: ¹H NMR (CDCl₃) δ 7.44–7.36 (m, 3H), 7.32–7.30 (m, 2H), 7.26–7.22 (m, 2H), 7.18–7.13 (m, 3H), 3.78 (s, 3H), 2.79–2.74 (m, 4H), 2.61–2.52 (m, 4H), 2.34–2.29 (m, 2H), 1.87 (q, 2H, *J* = 7.33 Hz), 1.74 (br t, 2H, *J* = 9.81 Hz), 0.95 (t, 3H, *J* = 7.33 Hz); ¹³C NMR (CDCl₃) δ 174.17, 174.08, 140.37, 139.46, 130.77, 129.40, 128.77, 128.72, 128.44, 126.09, 62.96, 60.49, 52.17, 50.01, 33.81, 33.71, 29.17, and 9.26.

Carfentanil (6.50 g) was taken up in isopropanol and treated with oxalic acid dihydrate (2.29 g, 18.17 mmol). The mixture was cooled, and the solids were collected by filtration. The solids were washed with cold isopropanol and diethyl ether and air-dried. The isolated solids were recrystallized from isopropanol to provide 4.50 g of carfentanil oxalate in a 45% yield from the protected amine 3. Carfentanil oxalate: mp 186–188 °C; ¹H NMR (CD₃OD) δ 7.52–7.44 (m, 3H), 7.37–7.35 (m, 2H), 7.30–7.19 (m, 5H), 3.80 (s, 3H), 3.53–3.48 (m, 2H), 3.34–3.23 (m, 4H), 2.99–2.95 (m, 2H), 2.50–2.45 (m, 2H), 1.97–1.89 (m, 4H), 0.92 (t, 3H, *J* = 7.33 Hz); ¹³C NMR (CD₃OD) δ 175.40, 172.62, 165.09, 138.21, 136.36, 130.15, 129.78, 129.36, 128.59, 128.48, 126.88, 60.42, 57.51, 51.91, 49.49, 30.31, 30.05, 28.48, and 8.13.

3.4 Carfentanil Citrate

Compound 3 (7.50 g, 18.10 mmol) was hydrogenated as described in Section 3.3 to generate compound 4. The free amine was alkylated and purified, also as described in Section 3.3. Carfentanil was treated with citric acid (2.70 g, 14.05 mmol) in isopropanol. The solution was placed in a refrigerator for 16 h. The precipitate was collected by filtration and washed with cold isopropanol. The collected solids were recrystallized from acetone to provide 5.60 g of carfentanil citrate in a 53% yield from protected amine 3. Carfentanil citrate: mp 150–152 °C; ¹H NMR (CD₃OD) δ 7.52–7.39 (m, 5H), 7.29–7.18 (m, 5H), 3.80 (s, 3H), 3.48–3.44 (m, 2H), 3.30–3.14 (m, 4H), 3.02–2.96 (m, 2H), 2.77 (d, 2H, *J* = 33.89 Hz), 2.72 (d, 2H, *J* = 33.43 Hz), 2.48–2.44 (m, 2H), 2.03–1.89 (m, 4H), 0.92 (t, 3H, *J* = 7.56 Hz); ¹³C NMR (CD₃OD) δ 178.11, 175.42, 173.52, 172.71, 138.27, 136.75, 130.27, 129.77, 129.34, 128.58, 128.52, 126.74, 73.02, 60.62, 57.55, 51.86, 49.19, 43.44, 30.41, 30.04, 28.49, and 8.14.

3.5

Remifentanil Oxalate

Compound 3 (7.5 g, 18.10 mmol) was hydrogenated as described in Section 3.3. The free amine 4 was taken up in 40 mL of acetonitrile, and methyl acrylate (3.07 g, 35.68 mmol) was added to the solution. The solution was heated under a nitrogen atmosphere in a 70 °C oil bath for 16 h. The volatiles were removed under reduced pressure. This material was chromatographed in two batches using a Grace Reveleris X2 flash chromatography system with a gradient elution that had 0–5% of 95/5 methanol/ammonium hydroxide in dichloromethane to provide 5.12 g of remifentanil. Remifentanil: ^1H NMR (CDCl_3) δ 7.42–7.38 (m, 3H), 7.30–7.28 (m, 2H), 3.78 (s, 3H), 3.63 (s, 3H), 2.65–2.58 (m, 4H), 2.44–2.34 (m, 4H), 2.28–2.24 (m, 2H), 1.86 (q, 2H, J = 7.33 Hz), 1.63–1.54 (m, 2H), 0.94 (t, 3H, J = 7.33 Hz); ^{13}C NMR (CDCl_3) δ 174.20, 174.08, 173.03, 139.47, 130.74, 129.41, 128.77, 62.83, 53.37, 52.19, 51.73, 49.72, 33.58, 32.20, 29.16, and 9.21.

Remifentanil was taken up in isopropanol and treated with oxalic acid dihydrate (1.88 g, 14.91 mmol). The mixture was cooled, and the solids were collected by filtration. The solids were washed with cold isopropanol and then diethyl ether and air-dried. The isolated solids were recrystallized from isopropanol to provide 5.83 g of remifentanil oxalate in a 69% yield from the protected amine 3. Remifentanil oxalate: mp 169–171 °C; ^1H NMR (CD_3OD) δ 7.52–7.45 (m, 3H), 7.36–7.34 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.47–3.25 (m, 6H), 2.79 (apparent t, 2H, J = 7.33 Hz), 2.47–2.43 (m, 2H), 1.98–1.89 (m, 4H), 0.92 (t, 3H, J = 7.33 Hz); ^{13}C NMR (CD_3OD) δ 175.39, 172.61, 170.64, 164.96, 138.20, 130.13, 129.77, 129.37, 60.29, 51.91, 51.37, 47.79, 30.23, 28.46, 28.31, and 8.12.

3.6

Remifentanil Hydrochloride

Compound 3 (6.00 g, 12.75 mmol) was hydrogenated, and the resulting compound 4 was treated with methyl acrylate as described in Section 3.5. Remifentanil was dissolved in a minimal amount of diethyl ether and treated with methanolic hydrogen chloride until it became acidic, as determined by the use of hydrated pH paper. The precipitate was filtered and the collected solids were recrystallized from methanol/diethyl ether to provide 3.65 g of remifentanil hydrochloride in a 69% yield from the protected amine 3. Remifentanil hydrochloride: mp 209–210 °C; ^1H NMR (CD_3OD) δ 7.60–7.49 (m, 3H), 7.39–7.37 (m, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 3.53–3.49 (m, 2H), 3.39–3.33 (m, 4H), 2.82 (apparent t, 2H, J = 7.33 Hz), 2.55–2.50 (m, 2H), 1.96–1.83 (m, 4H), 0.93 (t, 3H, J = 7.33 Hz); ^{13}C NMR (CD_3OD) δ 175.40, 172.37, 170.59, 138.09, 130.20, 129.78, 129.43, 60.13, 52.21, 51.96, 51.45, 50.01, 30.51, 28.46, 28.27, and 8.11.

4.

CONCLUSION

Carfentanil oxalate, carfentanil citrate, remifentanil oxalate, and remifentanil hydrochloride were synthesized on a multigram scale. Only one synthetic transformation in each route required flash chromatographic purification. All other purifications were accomplished either by salt formation, precipitation, or recrystallization.

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